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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,007	11/20/2003	Randolph Mellus Johnson	DURE-007CON2	9101

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EXAMINER	
GHALI, ISIS A D	

ART UNIT	PAPER NUMBER
1611	

MAIL DATE	DELIVERY MODE
11/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,007	JOHNSON ET AL.	
	Examiner	Art Unit	
	Isis A. Ghali	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-56,58-67,69-72,74-81,83-94 and 96-99* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-56,58-67,69-72,74-81,83-94 and 96-99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/26/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The receipt is acknowledged of applicants' request for RCE and IDS, both filed 08/26/2008.

Claims 57, 68, 73, 82, and 95 have been canceled by "Examiner Amendments" dated 06/27/2008.

Claims 48-56, 58-67, 69-72, 74-81, 83-94, 96-99 are pending and included in the prosecution.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 08/26/2008 has been entered.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 48-56, 58-67, 69-72, 74-81, 83-91 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for sufentanil as a fentanyl congener, does not reasonably provide enablement for fentanyl itself and any other fentanyl congener. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir.1988). Among these factors are: the nature of the invention; the breadth of the claims; the state of the prior art; the relative skill of those in the art; the amount of direction or guidance presented; the predictability or unpredictability of the art; the presence or absence of working examples; and the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The nature of the invention: The nature of the invention is a method for providing analgesia in a subject, said method comprising delivering a composition comprising fentanyl or a fentanyl congener to the subject wherein the composition is administered to the subject using an implantable convective delivery system for 48 hours or more. Nowhere in the specification had applicants showed treating pain using fentanyl or fentanyl congener other than sufentanil.

The breadth of the claims: The claims are broad. The claims encompass fentanyl and all its congeners including alfentanil and fentanyl. Fentanyl and alfentanil differ in their potency and consequently effective doses and period of action.

The state of the prior art: The state of the art does not recognize implantable convective delivery system comprising fentanyl or fentanyl congener at a concentration of about 0.5 mg/ml to about 500 mg/ml or greater, wherein the composition is administered to the subject using an implantable convective delivery system, and the fentanyl or its congener is delivered from the system at a low volume rate of about 2 ml/day or less. The state of the recognized that fentanyl and its congeners have different pharmacokinetics and delivered in different doses to obtain the analgesic effect. The article "Analgesia and sedation with sufentanil in intensive care medicine" by Wappler et al. at table 1, demonstrated that fentanyl and its congener have different lipid solubility and half life, plasma clearance, etc., and these variations will provide variations in their route of delivery, effective doses, duration of action, and analgesia they provide. Not all fentanyl and its congeners can be delivered by the same composition in the same concentration and delivery rates and not all expected to provide the same effect.

The relative skill of those in the art: The relative skill of those in the art is high.

The amount of direction or guidance presented: The specification provides no guidance, in the way written description, on treating pain by implantable convective device comprising fentanyl and its congeners at a concentration of 0.5-500 mg/ml delivered at rate of 2 ml/hr or less, other than sufentanil. The specification describes

sufentanil delivered in implantable convective device comprising sufentanil at a concentration of 0.5-500 mg/ml delivered at low volume rate of 2 ml/hr (examples 2-5). It is not obvious from the disclosure of sufentanil in implantable convective device at specific concentration delivered at specific rate if fentanyl and the other congeners will work for treating pain if delivered in the same devices at the same concentration and at the same delivery rate. Wappler et al. disclosed that sufentanil is more potent than fentanyl and its congeners and showed that fentanyl and its congeners have different pharmacokinetics. *In re Dreshfield*, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." A disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See *In re Riat* et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr et al*. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

The predictability or unpredictability of the art: The lack of guidance from the specification and from the prior art with regard to treating pain with fentanyl and congeners, other than sufentanil, makes practicing the claimed invention unpredictable in the terms of concentration and delivery rates of all of fentanyl and its congeners to provide systemic analgesia for at least 48 hours.

The presence or absence of working examples: The specification exemplified only sufentanil. No working examples to show using fentanyl or any other congeners. Therefore, the specification has enabled using sufentanil to treat pain by providing systemic analgesia in specific concentrations and delivery rates delivered from convective devices.

The quantity of experimentation necessary: The art demonstrates that sufentanil is more potent and has pharmacokinetics that differ from fentanyl and its other congeners. The specification disclosed only sufentanil at specific concentrations and delivery rates. Therefor, the practitioner would turn to trial and error experimentation to practice the instant method for treating pain using fentanyl or other congeners, other than sufentanil, without guidance from the specification or the prior art. Therefore, undue experimentation becomes the burden of the practitioner.

4. Claims 48-56, 58-62 and 92 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for sufentanil at a concentration of about 0.5 mg/ml to about 500 mg/ml, wherein the composition is administered to the subject using an implantable convective delivery system, and sufentanil is delivered from the system at a low volume rate of about 2 ml/day, does not reasonably provide enablement for sufentanil any other concentration other than between 0.5-500 mg/ml delivered at low volume rate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir.1988). Among these factors are: the nature of the invention; the breadth of the claims; the state of the prior art; the relative skill of those in the art; the amount of direction or guidance presented; the predictability or unpredictability of the art; the presence or absence of working examples; and the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The nature of the invention: The nature of the invention is a method for providing analgesia in a subject, said method comprising delivering a composition comprising fentanyl or a fentanyl congener to the subject wherein the composition is administered to the subject using an implantable convective delivery system; and fentanyl or its congener is delivered from the system for 48 hours or more at a low volume rate of 2 ml/day or less and is sufficient to provide systemic analgesia in the subject.

The breadth of the claims: The claims are broad. The claims encompass any doses and concentrations of fentanyl and its congeners ranging from portion of microgram to many grams included in each ml.

The state of the prior art: The state of the art does not recognize implantable convective delivery system comprising fentanyl or fentanyl congener (sufentanil) at a concentration of about 0.5 mg/ml to about 500 mg/ml and delivered at low volume rate

of 2ml/day or less. The state of the recognized sufentanil delivered at low delivery rate of 0.075 µg/kg/h to 2.5 µg/kg/h. See the article "Analgesia and sedation with sufentanil in intensive care medicine" by Wappler et al.

The relative skill of those in the art: The relative skill of those in the art is high.

The amount of direction or guidance presented: The specification provides no guidance, in the way written description, on treating pain by implantable convective device comprising sufentanil delivered at low volume rate of 2 ml/hr or less at any concentration other than concentration of 0.5-500 mg/ml or greater. In paragraph 0105 of the present disclosure, applicants disclosed that: "In general, the drug delivery devices suitable for use in the invention are those that can deliver drug at a low dose, e.g., for sufentanil from about 0.01 µg/hr to about 200 µg/hr, and preferably at a low volume rate e.g., on the order of nanoliters to microliters per day. In one embodiment, a volume rate of from about 0.01 µl/day to about 2 ml/day is accomplished by delivery of about 80 µl/hour over a period of 24 hours, with the delivery rate over that 24 hours period fluctuating over that period by about .+-.5% to 10%". The specification describes sufentanil delivered from implantable convective device comprising sufentanil at a concentration of 0.5-500 mg/ml delivered at rate of 2 ml/hr or less (examples 2-5). It is not obvious from the disclosure of sufentanil in implantable convective device at specific concentration delivered at specific rate if sufentanil at any other concentrations will work for treating pain if delivered from the same devices at the same delivery rate. *In re Dreshfield*, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ in their

properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." A disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See *In re Riat* et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr et al.* (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

The predictability or unpredictability of the art: The lack of guidance from the specification and from the prior art with regard to treating pain with sufentanil at concentration other than 0.5-500 mg/ml delivered at the low volume rate of 2 ml/day or less makes practicing the claimed invention unpredictable in the terms of other concentration and the same delivery rates.

The presence or absence of working examples: The specification exemplified only sufentanil at concentration of 0.5-500 mg/ml delivered at a low rate volume of 2 ml/day or less. No working examples to show using other concentration at the claimed delivery rate. Therefore, the specification has enabled using sufentanil at a concentration of about 0.5 mg/ml to about 500 mg/ml and delivered at low volume rate of 2ml/day to treat pain by providing systemic analgesia.

The quantity of experimentation necessary: The specification disclosed only sufentanil at specific concentrations and specific delivery rates. Therefor, the practitioner would turn to trial and error experimentation to practice the instant method

for treating pain using sufentanil without guidance from the specification or the prior art. Therefore, undue experimentation becomes the burden of the practitioner.

5. Claims 48-56, 58-67, 69-72, 74-82, 83, 92, 93, 96-99 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection. The claims are drawn to “2 ml/day or less”, and further claim 63 and claims that depends from claim 63 are drawn to “0.5-500 mg/ml or greater”. The specification gives no guidance to one of ordinary skill in the art regarding the expressions “less” or “greater”. The specification does not describe how much less or how much greater to set the limits to the scope of the ranges. In paragraph 0024 of the specification applicant describes the low volume rate “from about 0.01 µl/day to 2 ml/day so as to minimize tissue disturbance or trauma.” However the claims included open-ended lower limit that is less than 2 ml/day that can be as little as 0.0001 µl/day that may be too little to the desired purpose. The same for the concentration of the fentanyl or its congeners, in paragraphs 73, applicants described many concentrations of fentanyl, and mentioned the expression “and greater”, however, did not describe the expression greater in terms of how greater could it be. Applicants expression "greater" can be as high as several grams of fentanyl or its congeners.

The expressions "or less" and "or greater" without partial or complete description of any values does not convey to one of ordinary skill in the art that applicants were in possession of the claimed subject matter. The expressions are recited without any correlation does not meet the written description requirement for values less or greater as one of ordinary skill in the art could not recognize or understand the limits for the values. Claims employing expressions at the point of novelty, such as applicants', neither provide those elements required to practice the inventions, nor "inform the public" during the life of the patent of the limits of the monopoly asserted. The expressions could encompass wide variations of the values and applicants claimed expressions represent only an invitation to experiment regarding possible means.

To satisfy the Written description requirement, applicant must convey with reasonable clarity to one skilled in the art, as of the filing date that applicant were in possession of the claimed invention. *Vas-Cath Inc. v Mahurkar*, 19 USPQ 2d 1111. The invention is, for purpose of the "written description" inquiry, what ever is now claimed (see page 1117). The specification does not clearly allow person of ordinary skill in the art to recognize that [he or she] invented what is claimed (see *Vas-Cath* at page 116). One cannot describe what one has not conceived. See *Fiddes v Baird*, 30 USPQ2d 1481, 1483.

The test for determining compliance with the written description requirement is whether the disclosure of the application as **originally filed reasonably conveys to one skilled in the art that the inventor had the possession at the time of the later claimed subject matter, rather than the presence or absence of literal support in**

the specification for the claimed language. See *In re Kaslow*, 707 F 2d 1366, 1375 (Fed. Cir. 1983). See MPEP 2163.06.

The written description requirement prevents applications from using the amendment process to update the disclosure in their disclosures (claims or specification) during the pendency before the patent office. Otherwise applicants could add new matter to their disclosures and date them back to their original filing date, thus defeating an accurate accounting of the priority of the invention. See 35 USC 132. **The function of description requirement is to ensure that the inventor had possession, as of filing date of the application relied on, the specific subject matter claimed by the inventor.** See *Genetech*, 108 F 3d 1361, 1365 (Fed. Cir. at 1366, 78, 1999).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 84-91, 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over the article "Analgesia and sedation with sufentanil in intensive care medicine" by Wappler et al. combined with article "Long term spinal therapy in terminally ill cancer patients" by Wagemans et al.

Wappler et al. teach that the administration of sufentanil is suitable for intensive care patients for systemic sedation and analgesia without significant respiratory depression during spontaneous breathing. Sufentanil continuous infusion was provided in a dose between 0.075 to 2.5 µg/kg/hr with median of 0.6 µg/kg/hr. See 1st, 2nd and 5th pages of the translation. For the average person weighing 60 kg, the dose disclosed by Wappler that induces systemic analgesia will ranges from 4.5 µg/hr to 150 µg/hr. The present claim 84 recites 0.01 µg/hour to about 200 µg/hour. Therefore, the claimed range is met by the reference, and the range disclosed by the reference falls within the claimed range.

Wappler however does not teach delivery of fentanyl using implantable convective devices to provide continuous analgesia for prolonged periods.

Wagemans et al. teach long-term opioid therapy with minimal side effects and efficacy throughout the body and for different types of pain, i.e. systemic, with sufentanil

preferred analgesic (abstract). The analgesia is achieved by systemic absorption of the opioid (page 72, left column, last paragraph). The opioid is administered in its minimal effective dose (table 2, page 72). The analgesic is administered by implanted infusion pump for months or years and provides constant infusion rate (page 73, left column, second paragraph).

Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide systemic analgesia using sufentanil delivered at concentration of 4.5 μg/hr to 150 μg/hr as disclosed by Wappler et al., and deliver sufentanil using implantable infusion pump disclosed by Wagemans et al. One would have been motivated to do so because Wegemans et al. teach that implanted infusion pump delivers sufentanil for months or years and provides constant infusion rate, as desired by applicants. One would have reasonably expected success of providing systemic analgesia for prolonged period of times up to years with delivery rate of sufentanil from 4.5 μg/hr to 150 μg/hr.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis Ghali whose telephone number is (571) 272-0595. The examiner can normally be reached on Monday-Thursday, 7:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Isis A Ghali/
Primary Examiner, Art Unit 1611

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